Somatostatin receptor subtype 1 (SSTR1) active compounds and their use in therapy.

FIELD OF THE INVENTION

This invention relates to a group of novel somatostatin receptor subtype 1 (SSTR1) active compounds and pharmaceutical compositions comprising said compounds. Furthermore, the invention concerns the use of said compounds for the treatment or prevention of diseases or conditions responding to selective SSTR1 active compounds. Moreover, the invention concerns methods of targeting a tissue bearing SSTR1s either for tissue imaging or as carriers for drugs to be transported to said tissue.

BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details regarding the practice, are incorporated by reference.

Somatostatin is a cyclic peptide found endogenously in two major forms made up of 14 (SRIF-14) or 28 (SRIF-28) amino acids. The shorter SRIF-14 is identical in sequence to the C-terminal half of SRIF-28. Somatostatin is produced widely in the body and acts both systemically and locally to inhibit the secretion of various hormones, growth factors and neurotransmitters. The biological effects of somatostatin are mediated by a family of G protein-coupled receptors, of which five subtypes (SSTR1-5) have been cloned in humans (Reisine and Bell 1995; Patel 1999). The affinities of the two endogenous forms of somatostatin on the five subtypes are relatively similar, although SRIF-28 has been reported to have a moderate preference for the SSTR5. However, the five subtypes are differentially expressed in different tissues and do also show some differences in their interaction with a number of signalling pathways. Thus, the pleiotropic physiological responses mediated by somatostatin are a reflection of its widespread distribution and the existence of multiple receptor subtypes.

Based on their sequence similarities and their affinity profiles towards a number of octapeptide and hexapeptide somatostatin analogs, the five subtypes in the somatostatin receptor family form two receptor subfamilies:

One made up of SSTR2, SSTR3 and SSTR5 and another subfamily made up of SSTR1 and SSTR4. The former possesses high and the latter rather low affinity towards the aforementioned hexapeptide and octapeptide analogs (Hoyer et al. 1995). Due to the availability of high affinity and selective ligands, the physiology of the SSTR2,3,5 subfamily has been more thoroughly characterized and it appears that the 'classical' effects of somatostatin, such as very potent inhibition of growth hormone, insulin, glucagon and gastric acid release, are mediated either primarily or exclusively via members of this subfamily.

Even though the physiology and pathophysiology of the subtypes SSTR1 and SSTR4 are less well understood, a number of findings about the role of these subtypes have been described in scientific publications and the patent literature. US 6,124,256 reported that, given their localisation in the vascular wall and their time-related induction during the proliferative stage, SSTR1 and/or SSTR4 may be the optimal subtypes to prevent fibroproliferative vasculopathy via a somatostatin receptor based therapy. In agreement with this, Curtis et al. (2000) have described SSTR1 and SSTR4 to represent the predominant subtypes expressed in human blood vessels and have proposed the use of SSTR1- or SSTR4-selective agonists for the treatment of endothelial cell-mediated proliferative diseases. Aavik et al. (2002) have demonstrated that a purportedly SSTR1- and SSTR4-selective peptide analogue of somatostatin (CH-275) is able to prevent intimal hyperplasia after rat carotid denudation injury. Taken together, these findings may explain why two peptide analogues of somatostatin, octreotide and lanreotide, which possess very high preferences for the subtypes SSTR2 and SSTR5 but have rather low affinities for the subtypes SSTR1 or SSTR4, failed to show efficacy in clinical trials aiming at the prevention of restenosis after percutaneous transluminal angioplasty (Eriksen et al. 1995; van Essen et al. 1995).

Due to the fact that SSTR1 activation causes antiproliferative effects, SSTR1-selective agonists may be useful for the treatment of SSTR1 bearing tumors. For example, it has been described that SSTR1 receptors are expressed in prostate cancer (Sinisi et al. 1997; Reubi et al. 1997; Reubi et al.

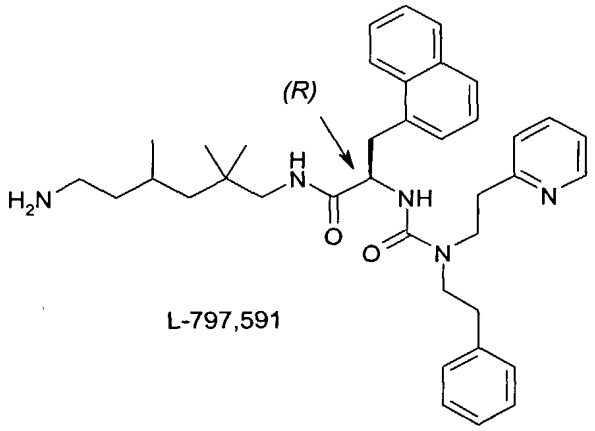
2001) but not in normal prostate tissue. Independent of its functional properties as an agonists or an antagonist, any SSTR1 selective ligand may be useful for the diagnosis of prostate tumors or tumors in other tissues expressing the SSTR1 subtype.

Somatostatin has a very short biological half-life and is therefore unsuitable for therapeutic use. A number of shorter hexa- and octapeptide analogs of somatostatin with improved biological stability have been identified (e.g. patent publications US 4,485,101, US 5,409,894 and WO 97/47317), but these abbreviated peptide analogs are heavily biased in favour of the SSTR2,3,5 subfamily and do not show any significant interaction with the subtypes SSTR1 or SSTR4. In contrast, WO 97/14715 and Rivier et al. (2001) describe a group of SSTR1 preferring undecapeptide agonists. However, besides their often rather short biological half-lives, peptides also possess other problematic properties, which make them unsatisfactory as medicines. For example, peptides have a very limited ability to penetrate membranes. This is one of the reasons, why it is in most cases impossible to apply peptides via an oral route and why peptides generally do not reach the central nervous system.

WO 97/03054 and US 6,221,870 describe benzo[g]quinoline-derived (WO 97/03054) or ergoline-derived (US 6,221,870) SSTR1-selective antagonist as lowering aggressive behavior in mice and, based on this observation, suggest such compounds to be useful for the treatment of depression, anxiety, affective disorders and attention deficit hyperactivity disorder.

Non-peptide somatostatin receptor ligands for all five somatostatin receptor subtypes have also been identified by Rohrer et al. (1998) through a strategy that consisted in the pharmacophore filtering of an existing compound collection in order to retrieve a subset of compounds which possessed structural features perceived to be critical for proper receptor-ligand interactions. The subsequent screening of this subset of compounds led to the discovery of an initial hit compound which then served as the starting point for a mix-and-split combinatorial chemistry campaign that resulted in the

generation of several hundred compound mixtures containing several hundred thousand molecules in total. Finally, the identification of selective compounds for each of the five somatostatin receptor subtypes was achieved by screening these complex mixtures against the receptor subtypes and deconvoluting libraries containing actives down to their individual components. For the somatostatin receptor subtype 1 this resulted in the identification of the SSTR1-selective compound L-797,591.



L-797,591

Importantly, the approach by Rohrer et al. (1998) relied on a generally accepted structure-activity notion concerning the essential amino acid residues in peptide analogs of somatostatin. By using a colour-coding scheme highlighting moieties of different molecules corresponding to each other, the authors of the paper make a particular point of emphasizing the fact that the structure-activity-relationship known from peptides does also hold for the peptidomimetics they discovered. It has long been recognized that the dipeptide unit made up of the two residues 8 (tryptophan) and 9 (lysine) in SRIF-14 are critical for high affinity binding to somatostatin receptors (cf Veber et al. 1979). While the tryptophan residue in position 8 shows some degree of flexibility, for example in that it can accommodate a D-Trp as well as an L-Trp enantiomer (Meyers et al. 1978), the substitution of the lysine in position 9, even by closely related basic amino acids such as ornithine or arginine, leads to large losses in affinity (Rivier et al. 1976). On the other hand, modulating the basic character of the lysine side chain by replacing it with a thialysine, a gamma- or a delta-fluorolysine did not result in a correlation between the pK_a's

of the side chains and the biological activities (Nutt et al. 1983). Based on this observation Nutt et al. (1983) concluded that deprotonation of the lysine side chain is not a requirement for biological activity. Kaupmann et al. (1995) went a step further and proposed a somatostatin receptor binding model, according to which a positive charge on lysine-9 in somatostatin actually is required in order to allow the formation of an ion pair with a negatively charged aspartate residue in the transmembrane domain 3 of the receptor. The fact that all five somatostatin receptor subtypes possess such a TM3 aspartate residue is in line with that proposal and suggests that the formation of an electrostatic interaction is a major contributor to the overall binding energy when a peptide analog of somatostatin or a peptidomimetic binds to somatostatin receptors. An important feature of the ligand-receptor interaction for somatostatin receptor would therefore appear to be analogous to the well-established binding model for biogenic amine receptor (Chen et al. 1999), according to which a high affinity ligand is required to contain a functional group that will provide for a positive charge when the ligand docks in the receptor binding site. The structure of all so far described molecules, which possess high affinity towards any of the five somatostatin receptor subtypes, independent of whether these molecules are peptides or peptidomimetics, are also supporting this binding interaction model, because all of these molecules contain a suitably basic functional group.

Surprisingly however, we have now found that the presence of a basic function that carries either a full or a partial positive charge at physiological pH values is not a mandatory requirement for a class of urea-based peptidomimetics in order for them to bind to the SSTR1 receptor. As a matter of fact, since it can be demonstrated that the presence or absence of such a basic function in molecules that are otherwise highly superimposable makes very little, if any, difference for their binding affinities on the SSTR1, it appears that at least this somatostatin receptor subtype is capable of operating in a binding mode that does not involve the formation of an ion pair between a positive charge in the ligand and the negative charge of a highly conserved aspartate residue in TM3.

OBJECTS AND SUMMARY OF THE INVENTION

The object of the present invention is to provide novel compounds, or more specifically, novel urea-based peptidomimetics possessing a high degree of selectivity towards the somatostatin receptor subtype 1 (SSTR1). A particular object is to provide novel compounds, the binding interaction of which to the SSTR1 is independent of the presence or absence of a basic function at physiological pH values.

Thus, according to one aspect, this invention concerns a novel compound of formula I as defined hereinafter or a pharmaceutically acceptable salt or ester thereof.

According to another aspect, this invention concerns a pharmaceutical composition comprising as active ingredient a novel compound of formula I as defined hereinafter or a pharmaceutically acceptable salt or ester thereof, and at least one pharmaceutically acceptable carrier.

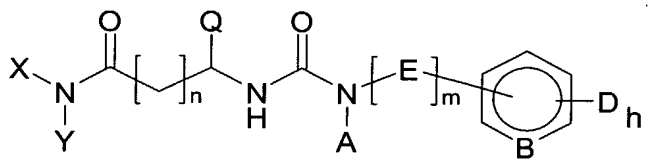
According to a third aspect, the invention concerns a compound of formula I as defined hereinafter or a pharmaceutically acceptable salt or ester thereof, for use in the manufacture of a pharmaceutical preparation for the treatment and/or prevention of a disease or condition responding to targeting with a selective SSTR1 compound.

According to a fourth aspect, the invention concerns the use of a compound of formula I as defined hereinafter or a pharmaceutically acceptable salt or ester thereof in combination with a detectable label, for targeting a tissue bearing SSTR1s for tissue imaging.

According to a fifth aspect, the invention concerns a compound of formula I as defined hereinafter or a pharmaceutically acceptable salt or ester thereof, for use as a carrier for another therapeutically active compound to be targeted to a tissue bearing SSTR1s.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides compounds of Formula I

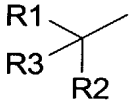


(I)

or a pharmaceutically acceptable salt or ester thereof, wherein

X is

1) H,
2) aryl,
3) heteroaryl or
4) a group of formula



;

wherein aryl and heteroaryl can be unsubstituted or substituted with 1 to 4 substituents selected from $\mathbf{R}^a$, as defined hereinafter;

Y is

1) H,
2) $(C_1\text{-}C_6)$alkyl,
3) $(C_3\text{-}C_7)$cycloalkyl or
4) $(C_3\text{-}C_7)$cycloalkyl-$(C_1\text{-}C_3)$alkyl;

Q is

1) aryl,
2) aryl-$(C_1\text{-}C_6)$alkyl,
3) heteroaryl or
4) heteroaryl-$(C_1\text{-}C_6)$alkyl;

wherein aryl and heteroaryl can be optionally substituted with 1 to 3 substituents selected from $\mathbf{R}^a$; and alkyl can be optionally substituted with Cy;

Cy is cycloalkyl, heterocyclyl, aryl or heteroaryl;

A is

1) $(C_1\text{-}C_6)$alkyl,
2) $(C_2\text{-}C_6)$alkenyl,
3) $(C_2\text{-}C_6)$alkynyl,
4) Cy or
5) Cy-$(C_1\text{-}C_6)$alkyl;

wherein alkyl and cycloalkyl can be optionally substituted with 1 to 2 substituents selected from R^c, as defined hereinafter; and Cy can be optionally substituted with 1 to 3 substituents selected from R^a;

B is

1) N or
2) C(D);

D is independently

1) H,
2) halogen,
3) $(C_1\text{-}C_6)$alkyl,
4) $(C_2\text{-}C_6)$alkenyl,
5) $(C_2\text{-}C_6)$alkynyl,
6) $-NR^bR^b$,
7) $-NO_2$ or
8) –CN;

wherein R^b is to be defined hereinafter;

E is

1) CH_2,
2) CHR^b or
3) CR^bR^c;

R1 is

1) H,
2) $(C_1\text{-}C_6)$alkyl,
3) $(C_2\text{-}C_6)$alkenyl,
4) $(C_2\text{-}C_6)$alkynyl,
5) Cy,
6) Cy-$(C_1\text{-}C_3)$alkyl,
7) $-(CH_2)_kC(O)NR^bR^b$ or
8) $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl;

wherein Cy can be unsubstituted or substituted with a group selected from R^a and alkyl, alkenyl, alkynyl and alkoxy can be unsubstituted or substituted with a group selected from R^c;

R2 is

1) H,
2) $(C_1\text{-}C_9)$alkyl,
3) $(C_2\text{-}C_9)$alkenyl,
4) $(C_2\text{-}C_9)$alkynyl,
5) Cy or
6) Cy-$(C_1\text{-}C_3)$alkyl;

wherein Cy can be unsubstituted or substituted with a group selected from **R^a** and alkyl, alkenyl and alkynyl can be unsubstituted or substituted with a group selected from **R^c**;

R3 is

1) H or
2) $(C_1\text{-}C_6)$alkyl;

R^a is independently

1) H,
2) halogen,
3) $(C_1\text{-}C_6)$alkyl,
4) $(C_2\text{-}C_6)$alkenyl,
5) $(C_2\text{-}C_6)$alkynyl,
6) Cy,
7) $-OR^b$,
8) $-SR^b$,
9) $-NR^bR^b$,
10) $-NR^bC(N)NR^bR^b$,
11) $-C(O)R^b$,
12) $-C(O)NR^bR^b$,
13) $-NC(O)R^b$,
14) $-SO_2NR^bR^b$,
15) $-NO_2$,
16) $-CN$,
17) $-CF_3$ or
18) amino-$(C_1\text{-}C_6)$alkyl;

R^b is independently

1) H,
2) $(C_1\text{-}C_6)$alkyl,
3) $(C_2\text{-}C_6)$alkenyl,
4) $(C_2\text{-}C_6)$alkynyl,
5) $(C_3\text{-}C_7)$cycloalkyl,
6) aryl,
7) heteroaryl,

or in the context of D, R1, R^a and R^c, **R^b** and **R^b** together with the atom to which they are attached can also form a 5 to 6 membered ring containing 1 to 2 heteroatoms selected from N, O and S;

R^c is independently

1) H,
2) halogen,
3) Cy,

4) –CN,
5) $-OR^b$,
6) $-SR^b$,
7) $-NR^bR^b$ or
8) $-NR^bC(N)NR^bR^b$;

k is an integer 0 or 1;

h is an integer from 0 to 4;

n is an integer 0 or 1; and

m is an integer from 0 to 3.

Certain compounds of formula (I), wherein A is 2-hydroxyethyl, have been disclosed in US 6,492,370 A1. Said compounds have, however, been used as intermediates only.

In the context of the current application "alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. The size of the alkyl can further be specified by adding the number of carbons in front of the group, e.g. $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_3)$alkyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, *neo*-pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. The size of the alkenyl can further be specified by adding the number of carbons in front of the group, e.g. $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_8)$alkenyl. Examples of alkenyl groups include, but are not limited to, vinyl, allyl, isopropenyl, 1-pentenyl, 2-pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. The size of the alkynyl can further be specified by adding the number of carbons in front of the group, e.g. $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_8)$alkynyl. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptenyl, and the like.

"Alkoxy" refers to an "alkyl", as defined above, which is appended to the parent molecular moiety via –O-, i.e. an ether bond. The size of the alkyl in the alkoxy can further be specified by adding the number of carbons in front of

the group, e.g. (C_1-C_6)alkoxy. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, tert-butoxy, and the like.

"Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 8 carbon atoms. The term also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. The size of the cycloalkyl can further be specified by adding the number of carbons in front of the group, e.g. (C_3-C_7)cycloalkyl, (C_5-C_{10})cycloalkyl. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. The term also includes aryl groups fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. The size of the aryl can further be specified by adding the number of carbons in front of the group, e.g. (C_6-C_{12})aryl. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydro-benzofuranyl, benzopyranyl, 1,4-benzodioxanyl, and the like.

"Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. The term also includes heteroaryl groups fused to a monocyclic cycloalkyl or monocyclic heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of heteroaryl groups include, but are not limited to, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Heterocyclyl" means mono- or bicyclic saturated rings containing at least one heteroatom selected from N, O, S, each of said ring having from 5 to 8 atoms in which the point of attachment may be carbon or nitrogen. The term also includes monocyclic heterocycles fused to an aryl or a heteroaryl group in which the point of attachment is on the non-aromatic portion. Furthermore, the term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- and 4-pyridones attached through the nitrogen. Other examples of heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl,

piperazinyl, imidazolinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroindanyl, and the like.

The term "cycloalkyl-alkyl", as employed herein, refers to a "cycloalkyl", as defined above, appended to the parent molecular moiety through an alkyl group, as defined above. The size of the cycloalkyl and the alkyl can further be specified by adding the number of carbons in front of the group, e.g. $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_5)$cycloalkyl$(C_1\text{-}C_2)$alkyl. Examples of cycloalkyl-alkyl include, but are not limited to, cyclohexylmethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, and the like.

The term "aryl-alkyl", as employed herein, refers to an "aryl", as defined above, appended to the parent molecular moiety through a $(C_1\text{-}C_6)$alkyl group, as defined above. The size of the aryl or alkyl can further be specified by adding the number of carbons in front of the group, e.g. aryl-$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{12})$aryl-$(C_1\text{-}C_3)$alkyl. Examples of aryl-alkyl include, but are not limited to, 2-naphthylmethyl, 1-(2- indanyl)ethyl, 2- tetrahydronaphthylethyl, and the like.

The term "heteroaryl-alkyl", as employed herein, refers to a "heteroaryl", as defined above, appended to the parent molecular moiety through an alkyl group, as defined above. The size of the alkyl can further be specified by adding the number of carbons in front of the group, e.g. heteroaryl-$(C_1\text{-}C_6)$alkyl, heteroaryl-$(C_1\text{-}C_2)$alkyl. Examples of heteroaryl-alkyl include, but are not limited to, 2-(2-pyridyl)propyl, 2-benzothiophenylmethyl, 4-(2-quinolyl)butyl, and the like.

The term "Cy-alkyl", as employed herein, refers to a "Cy", as defined above, appended to the parent molecular moiety through an alkyl group, as defined above. The size of the alkyl can further be specified by adding the number of carbons in front of the group, e.g. Cy-$(C_1\text{-}C_6)$alkyl, Cy-$(C_1\text{-}C_3)$alkyl. Examples of Cy-alkyl include, but are not limited to, benzyl, 1-(2-naphthyl)ethyl, 2-cyclohexylethyl, and the like.

The term "alkoxy-alkyl", as employed herein, refers to at least one "alkoxy", as defined above, appended to the parent molecular moiety through an alkyl group, as defined above. The size of the alkoxy and alkyl can further be specified by adding the number of carbons in front of the groups, e.g. $(C_1\text{-}C_3)$alkoxy-$(C_1\text{-}C_6)$alkyl. Examples of alkoxy-alkyl include, but are not limited to, methoxymethyl, propoxyethyl, *tert*-butoxypentyl, 3,3-dimethoxypropyl, and the like.

The term "amino-alkyl", as employed herein, refers to at least one amino group (i.e. $-NH_2$ group), appended to the parent molecular moiety through an alkyl group, as defined above. The size of the alkyl can further be specified by adding the number of carbons in front of the group, e.g. amino-(C_1-C_6)alkyl. Representative examples of amino-alkyl include, but are not limited to, aminomethyl, 2-aminoethyl, 1-aminoethyl, 2,2-diaminoethyl, 1-methyl-1-aminoethyl, and the like.

The term "halogen", as employed herein, refers to chlorine, bromine, fluorine or iodine.

The compounds of formula I, as well as the pharmaceutically acceptable salts and esters thereof, are referred to below as the compounds of the invention, unless otherwise indicated.

The invention includes within its scope all possible stereoisomers of the compounds, including geometric isomers, e.g. *Z* and *E* isomers (*cis* and *trans* isomers), and optical isomers, e.g. diastereomers and enantiomers. Furthermore, the invention includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting materials or they may be separated after the preparation of a mixture of isomers according to conventional separation methods, such as e.g. fractional crystallisation.

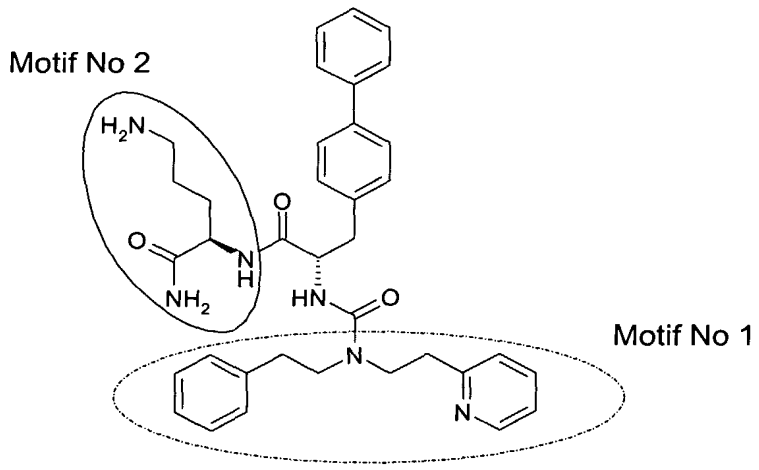
Some of the compounds may also exist as tautomers, namely having different points of attachment of hydrogen. For instance, ketones can exist also in their enol form (keto-enol tautomerism). The individual tautomers as well as mixtures thereof are encompassed within the compounds of the invention.

Pharmaceutically acceptable salts, e.g. acid addition salts with both organic and inorganic acids are well known in the field of pharmaceuticals. Non-limiting examples of these salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates and ascorbates. Pharmaceutically acceptable esters, when applicable, may be prepared by known methods using pharmaceutically acceptable acids that are conventional in the field of pharmaceuticals and that retain the pharmacological properties of the free form. Non-limiting examples of these esters include esters of aliphatic or aromatic alcohols, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl esters.

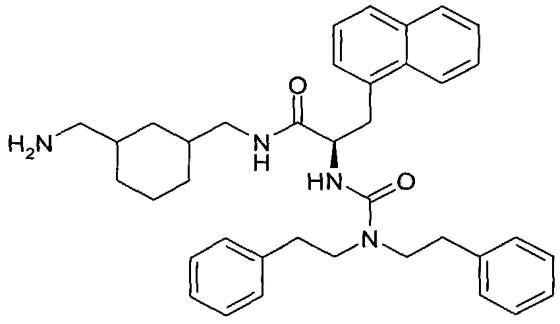
The compounds of the present invention possess selectivity towards the somastotatin receptor subtype 1 (SSTR1) and are therefore valuable for

the treatment and/or prevention of diseases or conditions, where SSTR1 agonists or antagonists are indicated to be useful.

The compounds of the current invention can be viewed as consisting of two different motifs constructed around an 'aromatic amino acid'. The *N*-alpha of the 'aromatic amino acid' is part of a urea function whereas the remaining half of the urea is formed with a 'secondary amine' (motif No 1). The structure of the compounds of the invention is completed via amidation of the 'aromatic amino acid' with motif No 2. Thus, the compounds of the invention are named as amides wherein the selection of the core amide depends on the structure of the motif No 2, i.e. the core amide is either the motif No 2 or the amidated 'aromatic amino acid'. The naming is further exemplified with the following structures:



(2*R*, 2'*S*)-5-Amino-2-{3'-biphenyl-4-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide



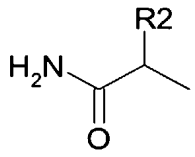
(2*R*)-*N*-(3-Aminomethylcyclohexylmethyl)-2-(3,3-diphenethylureido)-3-naphthalen-1-ylpropionamide

One preferred embodiment of the compounds of the formula I are those wherein E is $-CH_2-$, m is an integer 2 and B is N.

Another preferred embodiment of the compounds of formula I are those wherein Q is aryl-(C_1-C_6)alkyl or heteroaryl-(C_1-C_6)alkyl, and even more preferably an aryl-methyl or a heteroaryl-methyl. For this purpose, a preferred aryl and heteroaryl is naphthyl and indoyl, which can be optionally substituted with 1 to 2 groups selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halogen and $-CF_3$.

Another preferred embodiment of the compounds of formula I are those wherein the carbon to which the substituent Q is attached has the absolute configuration *R*.

Yet another preferred embodiment of the compounds of formula I are those wherein Y is hydrogen and X is a group of formula



, wherein R2 is as defined above or even more preferably, for this purpose R2 is (C_1-C_6)alkyl substituted with a group selected from R^c.

Yet another preferred embodiment of the compounds of the formula I are those wherein R2 is (C_1-C_6)alkyl.

Yet another preferred embodiment of the compounds of the formula I are those wherein n is 0.

Yet another preferred embodiment of the compounds of the formula I are those wherein h is 0.

The wording "SSTR1 selective" shall be understood to include compounds having a binding affinity constant K_i of at least 10 times better for the somatostatin receptor subtype 1 than for any of the other somatostatin receptor subtypes.

The tem "treatment" or "treating" shall be understood to include complete curing of a disease or condition, as well as amelioration or alleviation of said disease or condition.

The term "prevention" shall be understood to include complete prevention, prophylaxis, as well as lowering the individual's risk of falling ill with said disease or condition.

Determination whether a certain compound is an SSTR1 agonist or an SSTR1 antagonist can be carried out according to known methods, such as those described by Sato et al. (1995) and Jasper et al. (1998).

Typical diseases or conditions that can be treated or prevented by the use of the compounds of this invention are

1. Indications relating to diseases or conditions of central nervous system, such as anxiety, depression, schizophrenia, attention deficit hyperactive disorder and neurodegenerative diseases such as dementia, Alzheimer's disease and Parkinson's disease. The affective disorders includes bipolar disorders, e.g. manic-depressive psychoses, extreme psychotic states e.g. mania and excessive mood swings for which a behavioural stabilization is being sought. The anxiety states include generalized anxiety as well as social anxiety, agoraphobia and those behavioural states characterized by social withdrawal, e.g. negative symptoms;
2. Diseases or conditions benefiting from the use of anti-proliferative agents (e.g. involving pathological vascular proliferation), such as angiogenesis, restenosis, smooth muscle proliferation, endothelial cell proliferation and new blood vessel sprouting or conditions involving neovascularization. The angiogenic disease may for example be age-related macular degeneration or vascular proliferation associated with surgical procedures, e.g. angioplasty and AV shunts. Other possible indications are the treatments of arteriosclerosis, plaque neovascularization, hypertrophic cardiomyopathy, myocardial angiogenesis, valvular disease, myocardiac infarction, coronary collaterals, cerebral collaterals and ischemic limb angiogenesis;
3. Pathological conditions in the retina and/or iris-ciliary body, such as high intraocular pressure (IOP) and/or deep ocular infections. Such diseases may for instance be glaucoma, stromal keratitis, iritis, retinitis, cataract and conjunctivitis. Other diseases connected to the eye may be ocular and corneal angiogenic conditions, for example, corneal graft rejection, retrolental fibroplasia, Osler-Webber Syndrome or rubeosis;
4. Diabetic complications, such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension;
5. Cancers or excessive proliferation of normal or malignant tissue, such as the proliferation of adenoma cells, thyroid cancer, large

bowel cancer, breast cancer, prostatic cancer, benign prostatic hyperplasia, small cell lung cancer, non-small cell cancer, pancreatic cancer, stomach cancer, GI tumors, cholangiocarcinoma, hepatic cancer, vesical cancer, ovarian cancer, melanoma, osteosarcoma, chondrosarcoma, malignant pheochromocytoma, neuroblastoma, brain tumors, thymoma, paragangliomas, prostate carcinomas, sarcomas, gastroenteropancreatic tumors, gastric carcinomas, phaeochromocytomas, ependymomas, renal cancers, leukemia e.g., leukemia of basophilic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin disease and non-Hodgkin lymphoma;

6. Or wound healing, ovulation, menstruation, placentation, peptic ulcers, psoriasis, rheumatoid arthritis and Crohn's disease.

It should be stressed that the diseases or conditions listed under points 1-6 above are examples only. The use of the compounds is not limited to treatment and/or prevention of said exemplified diseases or conditions.

It will be appreciated by the expert in the field, which indications would benefit from the use of an SSTR1 agonist and which ones will benefit from the use of an SSTR1 antagonist.

The compounds according to this invention can also be used for targeting a tissue bearing SSTR1s in tissue imaging for diagnostic purposes *in vitro* or *in vivo*. In this case the compound shall be coupled to a detectable label. Examples of such labels are different isotopes, such as 123-I, 125-I, 111-In, 11-C etc., or fluorescent labels. The label can be coupled directly to the compound or to a suitable spacer, which in turn is coupled to the compound. Brain, vessels and tumors are examples of tissues and organs that possess SSTR1 receptors and which thus could be imaged with SSTR1 selective compounds according to this invention.

The compounds according to this invention can also, based on their high affinity for the SSTR1 receptor, be used as carrier for another therapeutically active compound to be targeted to tissues bearing SSTR1 receptors. Also in this case the other therapeutically active compound can be conjugated directly with the compound of this invention. Alternatively, said therapeutically active compound may be conjugated to a suitable spacer, which in turn is conjugated with the compound of this invention. This would

offer a useful means for transporting e.g. anti-cancer drugs to tissues bearing SSTR1 receptors.

Preferred diseases or conditions to be treated or prevented with the compounds of the invention are anxiety, depression, schizophrenia, attention deficit hyperactive disorder and neurodegenerative diseases such as dementia, Alzheimer's disease and Parkinson's disease; and even more preferably schizophrenia.

Another group of preferred diseases or conditions to be treated or prevented with the compounds of the invention are cancers or excessive proliferation of normal or malignant tissue, and even more preferably prostatic cancer, benign prostatic hyperplasia, pancreatic cancer, thyroid cancer, brain tumors and GI tumors.

Another group of preferred diseases or conditions to be treated or prevented with the compounds of the invention are diabetic complications, and even more preferably diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

Yet other preferred diseases or conditions to be treated or prevented with the compounds of the invention are those involving pathological vascular proliferation, and even more preferably said disease or condition is angiogenesis, restenosis, smooth muscle proliferation, endothelial cell proliferation, new blood vessel sprouting or neovascularization.

The pharmaceutical compositions of the compounds of the invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Formulations may for instance enable oral, buccal, topical, intranasal, parenteral (e.g. intravenous, intramuscular or subcutaneous) or rectal administration or administration by inhalation or insufflation. Compounds of the invention may also be formulated for sustained delivery.

For oral administration, forms of suitable compositions include but are not limited to tablets, chewable tablets and capsules. These may be prepared by conventional means with pharmaceutically acceptable excipients, such as binding agents (e.g. pregelatinized maize starch), disintegrants (e.g. potato starch), fillers (e.g. lactose) or lubricants (e.g. magnesium stearate). Tablets may be coated by methods well known in the art. For oral administration, possible liquid preparations include but are not limited to solutions, syrups or suspensions, or they may exist as dry powder for constitution with water or other suitable vehicle prior to use. These liquid

preparations may be prepared by conventional means with pharmaceutically acceptable agents, such as suspending agents, non-aqueous vehicles, preservatives and emulsifiers.

A possible dose of the active compounds of the invention for oral, parenteral, buccal or topical dose to an adult human is between 0.1 and 500 mg of the active compound per unit dose, which may be administered, for instance, 1 to 4 times a day.

It is well recognized that the precise dose, the route of administration and the dosing interval can be determined by those skilled in the art. It is also well recognized that these variables depend on multiple factors including but not restricted to the activity of the therapeutic compound, the formulation thereof, pharmacokinetic properties (such as absorption, distribution, metabolism and excretion) of the therapeutic compound, the nature and location of the target tissue or organ and the issues connected to the state of a disease or disorder in a patient in need of treatment. Additionally, when the compounds of the invention are administered with additional pharmaceutically active ingredients, one or more pharmaceutical compositions may be used for the delivery of all the agents, which may be administered together, or at different times, as determined by those skilled in the art.

The invention will be illuminated by the following non-restrictive Experimental Part.

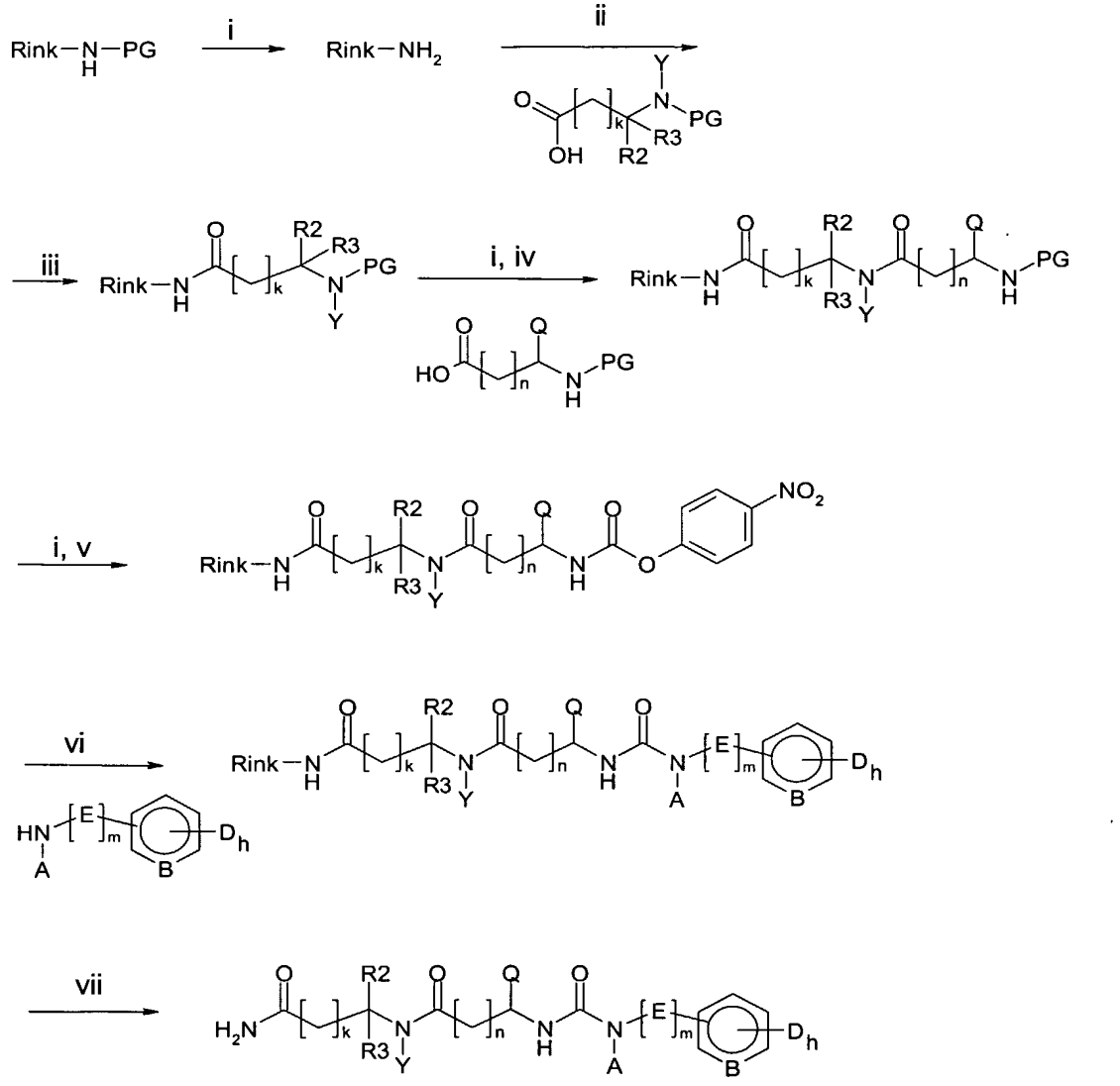
EXPERIMENTAL PART

List of abbreviations

ACN	acetonitrile
Boc	*tert*-butyloxycarbonyl
BSA	bovine serum albumin
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
DCM	dichloromethane
DCC	dicyclohexylcarbodiimide
DIC	diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
EDTA	ethylenediamine-tetraacetic acid
ESI	electrospray ionization
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HEPES	*N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
LC	liquid chromatography
MS	mass spectrometry
PG	protecting group
RP-HPLC	reversed-phase high performance liquid chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMOF	trimethyl orthoformate
TMS	tetramethylsilane
TRIS	tris(hydroxymethyl)aminomethane

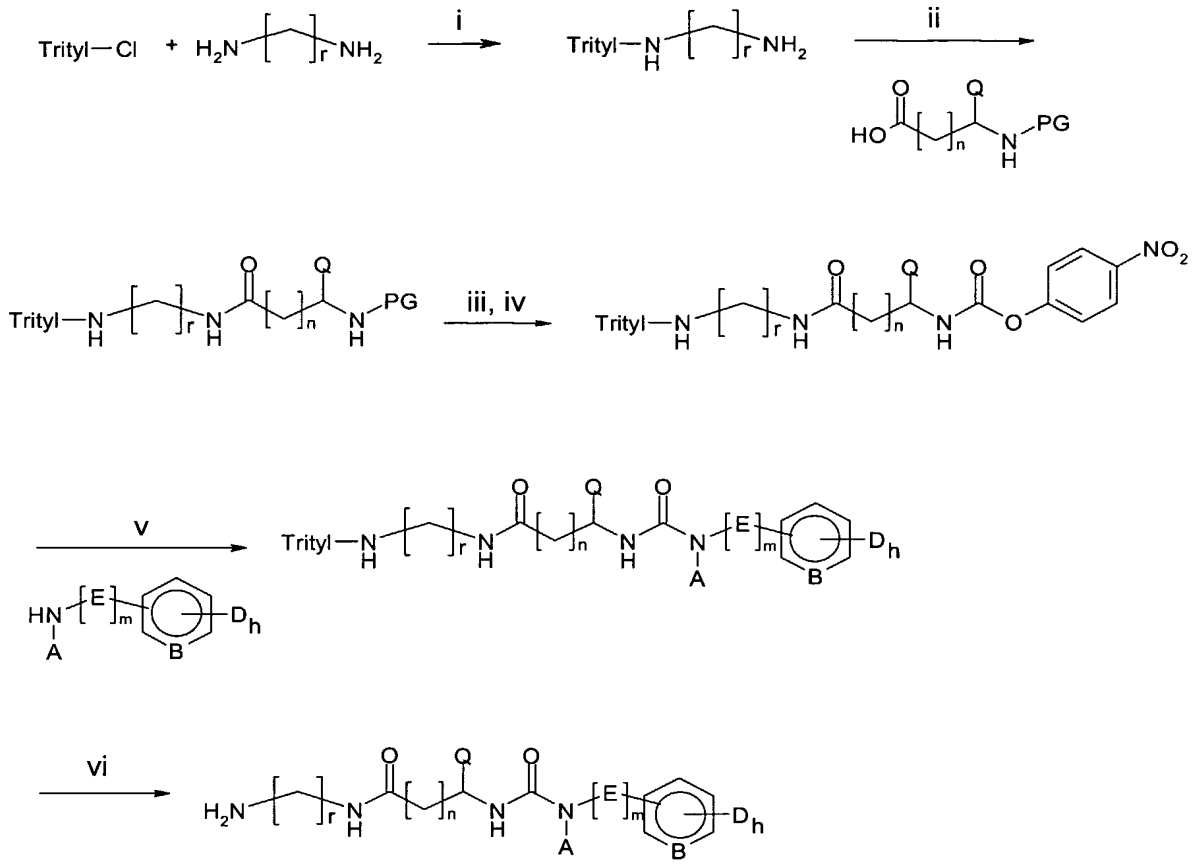
Compounds of the invention can be prepared using the following general synthetic schemes.

Scheme 1. Solid phase synthesis scheme I for the compounds of the invention



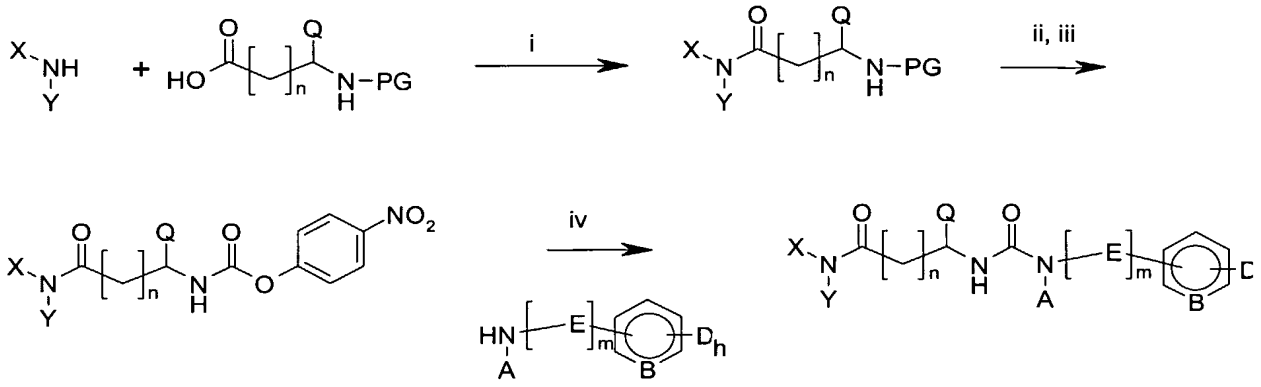
i) Removal of PG; ii) DIC, THF/DCM; iii) Ac_2O/pyridine/DCM; iv) DIC, DMF; v) 4-nitrophenyl chloroformate, DIPEA, THF/DCM (3:1); vi) urea formation by amine addition, DIPEA, DMF; vii) TFA/DCM

Scheme 2. Solid phase synthesis scheme II for the compounds of the invention



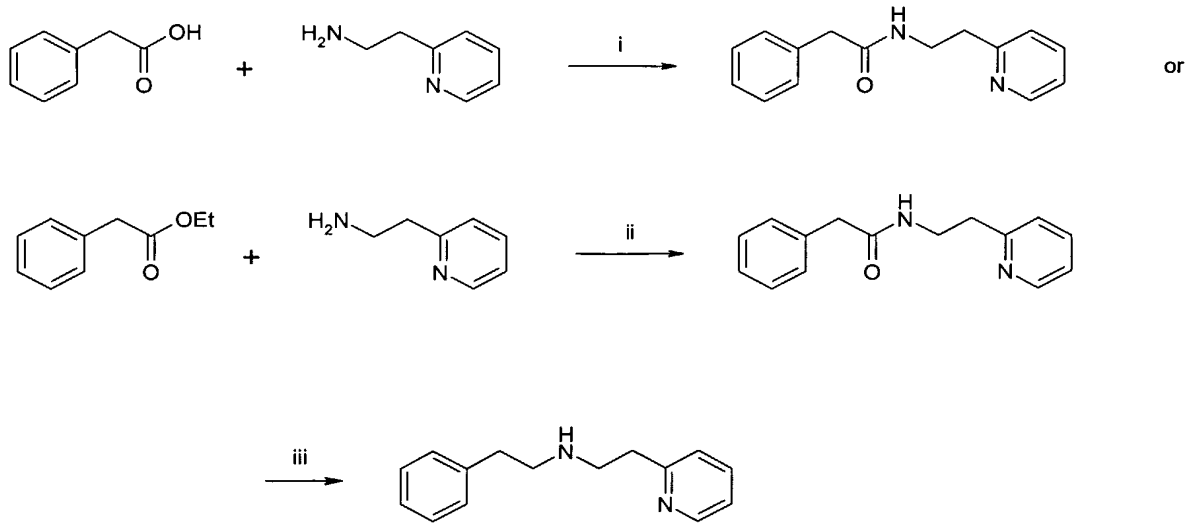
i) DCM; ii) DIC, DMF; iii) removal of PG; iv) 4-nitrophenyl chloroformate, DIPEA, THF/DCM (3:1); v) urea formation by amine addition, DIPEA, DMF; vi) 3 % TFA/DCM. r = 2-6.

Scheme 3. Solution phase synthesis scheme for the compounds of the invention



i) DIC, HOBt, DMF/DCM ; ii) removal of PG; iii) 4-nitrophenyl chloroformate, DIPEA, THF(dry); iv) urea formation by amine addition, THF

Scheme 4. Building block synthesis scheme for secondary amines



i) DCC, DCM; ii) 200°C (microwave), 10 min, neat; iii) 1M Borane-THF, THF, refluxing

It's evident for a person skilled in the art that the presented general schemes can be further modified for example by using different protecting

groups (e.g. those described in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed. Wiley, 1991, New York, US), or by adding or removing steps in between or after the described steps, which enable additional synthetic modifications to the examples given.

Starting materials

Rink and Trityl resins were obtained from Advanced ChemTech, UK. The amino acid derivatives were purchased from Novabiochem, Switzerland and PepTech Co., USA. DIC, HOBt and piperidine were products of Acros Organics, Belgium. DIPEA was from Fluka AG, Germany. All the other reagents or solvents were purchased from Aldrich or Merck, Germany, if not otherwise specified. The reagents were used as such and solvents were purified and dried according to the methods described in W.L.F. Armareggo and D.D. Perrin, "Purification of Laboratory Chemicals", 4th ed. Butterworth-Heinemann, 1996, Bath, Great Britain.

MS analysis

Molecular weights of the compounds were determined with a Micromass Micro triple quadrupole mass spectrometer. Essential MS parameters were: cone voltage 30 V, capillary voltage 3.5 kV, low mass resolution on MS1 15, high mass resolution on MS1 15, ion energy on MS1 1.0, source temperature 110 °C, desolvation temperature 250 °C and desolvation gas flow 700 l/h. Samples were introduced by a Waters Alliance 2695 HPLC. Flow rate of 0.3 ml/min was formed of 10% water and 90% MeOH eluent (containing 0.01% HCOOH). Sample volumes of 10 µl were injected through a Waters Symmetry Shield 2.1 X 10 mm C_{18} precolumn.

LC-MS analysis

For LC-MS analysis the gradient started from 100% water (containing 0.01% HCOOH) (A) which was changed linearly over ten minutes to 100% ACN (containing 0.01% HCOOH) (B). In addition, the Waters Symmetry Shield 2.1 X 50 mm C_{18} column with a corresponding precolumn was flushed for two minutes with B. The flow rate was 0.4 ml/min and sample volumes of 10 µl were injected. Some essential MS parameters were increased compared to standard MS analysis: desolvation temperature to

350°C and desolvation gas flow to 900 l/h. UV chromatograms were recorded with a Waters 996 diode array detector.

NMR analysis

NMR spectra for ^1H were recorded on a Bruker DMX 500 spectrometer operating at 500.13 MHz. CD_3OD or $CDCl_3$ were used as solvents and TMS as internal standard. In case of the product being a mixture of diastereomers, only the signals corresponding to one of the diasteromers are given.

Flash Chromatography purification

Flash Chromatographic purification was conducted with an Argonaut FlashMaster II Automated Purification System (Argonaut Technologies, UK) using normal phase columns (Supelco DSC-Si 20 g). The flow rate was 10 ml/min and the detection wavelength 254 nm. The standard elution program had a run time of 25 minutes with the following gradient: 100% DCM for 3 minutes, followed by gradual increase to 25% MeOH during 17 minutes and a gradual increase to 100% MeOH during the final 5 minutes. After MS verification, fractions containing the product were combined and evaporated.

RP-HPLC purification

Semi-preparative RP-HPLC purifications were done with a Waters 616 pump, controlled by a Waters 600 controller unit. The instrument was equipped with a Waters 2487 UV detector and a Waters fraction collector. An Xterra Prep C_{18} RP 10 X 150 mm column with 7.8 X 20 mm precolumn was used for purifications. The flow rate was 6.6 ml/min and the detection wavelength 254 nm. The gradient started with water (containing 0.3% HCOOH) (A) and was linearly changed to ACN (containing 0.3% HCOOH) (B) within ten minutes. In addition, the column was flushed with B for two minutes. The fraction collector was programmed to collect 30 s fractions. The fractions were analysed by MS.

LC purity analysis

HPLC purity of the compounds was determined using a Waters 616 pump, controlled by a Waters 600 controller unit. The instrument was further equipped with a Waters 2487 UV detector (detection wavelengths 254 nm and 220 nm). A Waters Symmetry Shield 2.1 X 50 mm C_{18} column with a corresponding precolumn and a flow rate of 0.4 ml/min was used. A linear

gradient starting with water (containing 0.01% HCOOH) (A) and ending with acetonitrile (containing 0.01% HCOOH) (B) over 17 minutes was applied, followed by maintaining solvent B for another minute.

Microwave reactions

Microwave assisted reactions were done in sealed, temperature-controlled and pressure-monitored reaction vessels in a Smith Creator microwave synthesis instrument from Personal Chemistry, Sweden. The instrument regulates the microwave power output according to the temperature and pressure achieved in the reaction vessel. Typical reaction times were around 10 minutes in a temperature of 200 °C.

Examples

The following representative compounds of the invention illustrate, but are not meant to limit, the scope of the invention.

Example 1

Synthesis of (2*R*, 2'*R*)-5-amino-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide, Compound 1

Step I

Rink amide resin (0.8 g, 0.7 mmol/g, 0.56 mmol) was washed with DMF prior to use. Washed resin was dissolved in 40 ml of 20 vol-% piperidine in DMF and the mixture was agitated for 30 minutes. The piperidine treatment was repeated with fresh solution. The resin was then washed twice with DMF, twice with DCM and twice with diethyl ether.

Step II

N_α-Fmoc-N_δ-Boc-D-Ornithine (762.4 mg, 454.5 g/mol, 1.7 mmol, 3 eq) and DIC (266.4 µl, 126.2 g/mol, 0.806 g/cm^3, 1.7 mmol, 3 eq) were dissolved in dry THF/DCM (1:1, 32 ml) and after 10 minutes mixed with the resin. After 8 hours of agitation, the solvent was filtered out and a fresh solution of N_α-Fmoc-N_δ-Boc-D-Ornithine and DIC in dry THF/DCM was introduced. After an additional 5 hours, the solvent was again filtered out.

Step III

Possibly unreacted amino groups of the resin were acetylated with a solution consisting of acetic anhydride (8 ml, 102.09 g/mol, 1.087 g/cm^3, 85.2 μmol) and pyridine (16 ml, 79.1 g/mol, 0.98 g/cm^3, 0.20 mmol) in dry DCM (16 ml) for 30 minutes. The resin was then filtered and washed three times with DMF, three times with DCM, and three times with MeOH.

Step IV

The *N*-alpha-Fmoc protection of the attached ornithine was removed according to the procedure described in step I but without any washes prior to the treatment with piperidine/DMF.

Step V

Fmoc-3-naphthalen-1-yl-D-alanine (736.0 mg, 437.49 g/mol, 1.68 mmol, 3 eq) and DIC (266.4 μl, 126.2 g/mol, 0.806 g/cm^3, 1.7 mmol, 3 eq) were dissolved in dry DMF (32 ml) and after 10 minutes mixed with the resin. After 3 hours of agitation, the solvent was filtered out and a fresh solution of Fmoc-3-naphthalen-1-yl-D-alanine and DIC in dry DMF was introduced. After an additional 3 hours, the solvent was again filtered out.

Step VI

The *N*-alpha-Fmoc protection of the naphthylalanine attached in step V was removed according to the procedure described in step I but again without any washes prior to the treatment with piperidine/DMF.

Step VII

4-Nitrophenyl chloroformate (450.4 mg, 201.56 g/mol, 2.2 mmol, 4 eq) and DIPEA (384.0 μl, 129.3 g/mol, 0.755 g/ml, 2.2 mmol, 4 eq) were dissolved in dry THF/DCM (3:1, 32 ml) and mixed with the resin. After two hours of agitation, the solvent was filtered and the resin washed once with DCM.

Step VIII

Phenethyl(2-pyridin-2-ylethyl)amine (example 16, 709.6 mg, 226.32 g/mol, 3.1 mmol, 5.6 eq) and DIPEA (336.0 μl, 129.3 g/mol, 0.755 g/ml, 1.96 mmol, 3.5 eq) were dissolved in dry DMF (32 ml) and mixed with the resin. After overnight agitation, the solvent was filtered and the resin washed three times with DMF, three times with DCM and once with 3 vol-% TFA in DCM.

Step IX

The resin bound product was cleaved and the Boc protection removed by treating the resin with 50 vol-% TFA in DCM (32 ml) for 30 min after which the resulting red solution was collected and the resin was washed once with DCM. Water (8 ml) was added to the combined fractions and the solvents were evaporated. The product was purified using preparative RP-HPLC purification to obtain the title compound with 21 % yield.

MS-ESI$^+$ (m/z): 581 $[M+H]^+$, 291 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.40 (1H, m), 8.21 (1H, m), 7.86 (1H, d, J = 7.87 Hz), 7.75 (1H, d, J = 7.87 Hz), 7.69-7.65 (1H, m), 7.55 (1H, m), 7.49-7.46 (1H, m), 7.43 (1H, m), 7.38-7.35 (1H, m), 7.22-7.03 (7H, m), 4.59-4.56 (1H, m), 4.39 (1H, m), 3.69-3.65 (1H, m), 3.49-3.38 (2H, m), 3.32-3.25 (1H, m), 3.21-3.15 (1H, m), 2.92 (2H, m), 2.76 (2H, m), 2.59-2.56 (2H, m), 1.95-1.91 (1H, m), 1.74-1.67 (4H, m).

Example 2

Synthesis of (2*R*,2'*R*)-5-isopropylamino-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide, Compound 2

(2*R*,2'*R*)-5-Amino-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide (example 1, 38.7 mg, 580.73 g/mol, 66.6 μmol) was dissolved in TMOF (0.5 ml) and DIPEA (15.6 μl, 129.25 g/mol, 0.755 g/ml, 91.1 μmol, 1.4 eq) was added. Acetic acid (7.0 μl, 0.7 vol-% of tot.vol.) and acetone (7.0 μl, 58.08 g/mol, 0.79 g/ml, 95.2 μmol, 1.4 eq) were added and the mixture stirred for 15 min after which $NaBH(OAc)_3$ (25.5 mg, 211.94 g/mol, 0.12 mmol, 1.8 eq) in TMOF (0.5 ml) was added and the reaction mixture stirred over night. Unreacted $NaBH(OAc)_3$ was quenched with a few drops of water and the mixture was evaporated to dryness. Water was added to the residue and the product was extracted with ethyl acetate. The combined fractions were dried over Na_2SO_4. 30 mg of crude product was obtained and it was further purified using preparative RP-HPLC purification to obtain the title compound with 24 % yield.

MS-ESI$^+$ (m/z): 623 $[M+H]^+$, 312 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.42 (1H, m), 8.25-8.22 (2H, m), 7.88 (1H, d, *J* = 8.04 Hz), 7.77 (1H, d, *J* = 8.04 Hz), 7.69-7.66 (1H, m), 7.58-7.55 (1H, m), 7.51-7.48 (1H, m), 7.45 (1H, m), 7.40-7.37 (1H, m), 7.23-7.20 (3H, m), 7.17-7.13 (1H, m), 7.10-7.05 (2H, m), 4.61-4.58 (1H, m), 4.44-4.41 (1H, m), 3.72-3.68 (1H, m), 3.52-3.48 (1H, m), 3.45-3.39 (1H, m), 3.36-3.26 (2H, m), 3.23-3.17 (1H, m), 3.23-3.17 (1H, m), 3.04-2.96 (2H, m), 2.79-2.76 (2H, m), 2.62-2.58 (2H, m), 1.98-1.93 (1H, m), 1.79-1.71 (3H, m), 1.30 (6H, d).

Example 3

Synthesis of (2*S*,2'*R*)-4-methylsulfanyl-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}butyramide, Compound 3

The synthesis was carried out as in example 1, except that in step II Fmoc-L-methionine was used instead of N_α-Fmoc-N_δ-Boc-D-Ornithine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 29 % yield.

MS-ESI$^+$ (m/z): 598 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.59 (1H, m), 8.22-8.19 (1H, m), 8.13 (1H, d, *J* = 8.24 Hz), 8.07 (1H, br s), 7.88 (1H, d, *J* = 8.24 Hz), 7.78 (1H, d, *J* = 8.24 Hz), 7.67 (1H, m), 7.63 (1H, m), 7.59-7.55 (1H, m), 7.52-7.49 (1H, m), 7.43-7.36 (2H, m), 7.28-7.24 (2H, m), 7.21-7.18 (1H, m), 7.14 (2H, m), 4.44-4.40 (1H, m), 4.25-4.22 (1H, m), 3.65-3.60 (1H, m), 3.50-3.29 (4H, m), 3.10-3.00 (2H, m), 2.77-2.68 (2H, m), 1.96 (3H, s), 1.94-1.81 (4H, m), 1.59-1.52 (1H, m).

Example 4

Synthesis of (2*S*,2'*R*)-3-methyl-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}butyramide, Compound 4

The synthesis was carried out as in example 1, except that in step II Fmoc-L-valine was used instead of N_α-Fmoc-N_δ-Boc-D-Ornithine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 22 % yield.

MS-ESI$^+$ (m/z): 566 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.54 (1H, m), 8.17 (1H, m), 8.11-8.07 (1H, m), 8.07 (1H, br s), 7.86 (1H, d, *J* = 7.86 Hz), 7.75 (1H, d, *J* = 7.86 Hz), 7.60-7.55 (2H, m), 7.50-7.47 (2H, m), 7.42-7.37 (2H, m), 7.24-7.21 (2H, m), 7.18-7.15 (1H, m), 7.08 (2H, m), 4.65-4.60 (1H, m), 4.10 (1H, m), 3.58-3.51 (2H, m), 3.45-3.33 (2H, m), 3.28-3.24 (2H, m), 2.98-2.95 (2H, m), 2.67-2.63 (2H, m), 2.04-1.97 (1H, m), 0.69 (6H, t).

Example 5

Synthesis of (2*S*,2'*R*)-2-{2'-[3,3-bis(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}-4-methylsulfanylbutyramide, Compound 5

The synthesis was carried out as in example 1, except that in step II Fmoc-L-methionine was used instead of N_α-Fmoc-N_δ-Boc-D-Ornithine and in step VIII bis(2-pyridin-2-ylethyl)amine (example 17) was used instead of phenethyl(2-pyridin-2-ylethyl)amine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 33 % yield.

MS-ESI$^+$ (m/z): 599 $[M+H]^+$, 300 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.51 (2H, m), 8.15 (1H, m), 8.08 (1H, br s), 7.88-7.85 (3H, m), 7.78 (1H, m), 7.58-7.54 (1H, m), 7.51-7.48 (1H, m), 7.42-7.35 (6H, m), 4.47-4.44 (1H, m), 4.23 (1H, m), 3.61-3.44 (6H, m), 3.00-2.95 (4H, m), 1.99-1.92 (1H, m), 1.95 (3H, s), 1.89-1.79 (2H, m), 1.58-1.51 (1H, m).

Example 6

Synthesis of (2*R*)-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 6

The synthesis was carried out as in example 3, but without steps II and IV. Step III (capping) was done after step V (coupling of Fmoc-3-(1-naphthyl)-D-alanine to the resin). The product was purified using preparative RP-HPLC purification to obtain the title compound with 17 % yield.

MS-ESI$^+$ (m/z): 467 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.45 (1H, m), 8.24 (1H, m), 8.07 (1H, br s), 7.87-7.84 (2H, m), 7.75 (1H, m), 7.56-7.53 (1H, m), 7.49-7.46 (1H, m), 7.44 (1H, m), 7.40-7.36 (2H, m), 7.25 (1H, m), 7.21-7.18 (2H, m),

7.15-7.12 (1H, m), 7.02 (2H, m), 4.69-4.66 (1H, m), 3.69-3.65 (1H, m), 3.45-3.34 (4H, m), 3.22-3.16 (1H, m), 2.87-2.78 (2H, m), 2.59-2.56 (2H, m).

Example 7

Synthesis of (2*R*,2'*R*)-5-amino-2-{2'-[3-(2-cyclohexylethyl)-3-(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}pentanamide, Compound 7

The synthesis was carried out as in example 1, except that in step VIII (2-cyclohexylethyl)-(2-pyridin-2-ylethyl)amine (example 19) was used instead of phenethyl(2-pyridin-2-ylethyl)amine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 21 % yield.

MS-ESI$^+$ (m/z): 587 $[M+H]^+$, 294 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.43 (2H, m), 8.22 (1H, m), 7.88 (1H, m), 7.78 (1H, d, *J* = 7.81 Hz), 7.71-7.68 (1H, m), 7.58-7.55 (1H, m), 7.50 (1H, m), 7.43-7.38 (2H, m), 7.24 (1H, m), 7.15 (1H, m, *J* = 7.81 Hz), 4.59-56 (1H, m), 4.43-4.40 (1H, m), 3.72-3.68 (1H, m), 3.54-39 (3H, m), 3.07-3.00 (1H, m), 2.97-2.91 (2H, m), 2.86-2.83 (2H, m), 1.97-1.92 (1H, m), 1.77-1.53 (9H, m), 1.23-1.03 (6H, m), 0.83-0.76 (2H. m);

Example 8

Synthesis of (2*R*,2'*R*)-5-amino-2-{2'-[3-(2-dimethylaminoethyl)-3-(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}pentanamide, Compound 8

The synthesis was carried out as in example 1, except that in step VIII *N*,*N*-dimethyl-*N'*-(2-pyridin-2-ylethyl)ethane-1,2-diamine (example 22) was used instead of phenethyl(2-pyridin-2-ylethyl)amine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 9 % yield.

MS-ESI$^+$ (m/z): 549 $[M+H]^+$, 275 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.45 (1H, m), 8.36 (2H, br s), 8.23 (1H, m), 7.88 (1H, m), 7.78 (1H, m), 7.72-7.68 (1H, m), 7.58-7.55 (1H, m), 7.52-7.49 (1H, m), 7.47-7.45 (1H, m), 7.40-7.37 (1H, m), 7.25 (1H, m), 7.11 (1H, m), 4.61-4.58 (1H, m), 4.40-4.37 (1H, m), 3.75-3.71 (1H, m), 3.63-3.56

(1H, m), 3.53-43 (3H, m), 3.38-35 (1H, m), 2.97-2.73 (6H, m), 2.64 (6H, s), 1.98-1.92 (1H, m), 1.76-1.70 (3H, m);

Example 9

Synthesis of (2*R*,2'*R*)-5-amino-2-{2'-[3-[2-(4-aminophenyl)ethyl]-3-(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}pentanamide, Compound 9

The synthesis was carried out as in example 1, except that in step VIII 4-[2-(2-pyridin-2-ylethylamino)ethyl]phenylamine was used instead of phenethyl(2-pyridin-2-ylethyl)amine. The product was purified using preparative RP-HPLC purification to obtain the title compound with 32 % yield.

MS-ESI$^+$ (m/z): 597 $[M+H]^+$, 299 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.42 (1H, m), 8.36 (1H, br s), 8.23 (1H, m), 7.88 (1H, d, J = 7.89 Hz), 7.78 (1H, m), 7.69-7.66 (1H, m), 7.59-7.55 (1H, m), 7.52-7.48 (1H, m), 7.44 (1H, m), 7.40-7.37 (1H, m), 7.23-7.20 (1H, m), 7.10 (1H, d, J = 7.89 Hz), 6.82 (2H, m), 6.62 (2H, m), 4.58-4.55 (1H, m), 4.40 (1H, m), 3.69-3.65 (1H, m), 3.51-3.38 (2H, m), 3.33-3.28 (1H, m), 3.27-3.10 (2H, m), 2.94-2.91 (2H, m), 2.79-2.76 (2H, m), 2.50-2.46 (2H, m), 1.97-1.91 (1H, m), 1.75-1.65 (3H, m);

Example 10

Synthesis of (2*R*)-*N*-(4-aminobutyl)-3-(1*H*-indol-3-yl)-2-[3-(3-phenylpropyl)-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 10

Step I

Trityl chloride resin (0.15 g, 1.5 mmol/g, 0.225 mmol) was washed with DCM prior use. 1,4-Diaminobutane (0.226 ml, 88.15 g/mol, 0.877 g/ml, 2.25 mmol, 10 eq) in DCM (3 ml) was added to the resin and the mixture was agitated for 15 hours. The resin was then washed three times with DCM.

The subsequent steps in the synthesis were done as in example 1 steps V-IX, except that in step V N_α-Fmoc-$N_{(in)}$-Boc-D-tryptophan was used instead of Fmoc-3-(1-naphthyl)-D-alanine and in step VIII (3-phenylpropyl)-(2-pyridin-2-ylethyl)amine (example 20) was used instead of phenethyl(2-pyridin-2-ylethyl)amine. In step VIII the TFA-wash was not carried out and cleavage from the resin was achieved with 25 % TFA in DCM to remove the Boc-

protection from the tryptophan at the same time. The product was purified using preparative RP-HPLC purification to obtain the title compound with 31 % yield.

MS-ESI$^+$ (m/z): 541 $[M+H]^+$, 271 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.42 (1H, m), 7.83-7.80 (1H, m), 7.61 (1H, m), 7.39-7.36 (1H, m), 7.32 (1H, m), 7.25-7.13 (4H, m), 7.11 (5H, m), 4.46-4.43 (1H, m), 3.57-3.44 (2H, m), 3.30-3.05 (3H, m), 3.00-2.94 (1H, m), 2.89-2.85 (4H, m), 2.48-2.38 (2H, m), 1.69-1.45 (8H, m);

Example 11

Synthesis of (2*R*)-*N*-[2-(2-aminoethoxy)ethyl]-2-[3-butyl-3-(2-pyridin-2-ylethyl)ureido]-3-naphthalen-2-ylpropionamide, Compound 11

The synthesis was carried out as in example 10, except that 1,5-diamino-3-oxapentane was coupled to the resin instead of 1,4-diaminobutane. In step V Fmoc-3-(2-naphthyl)-D-alanine was used instead of N_α-Fmoc-$N_{(in)}$-Boc-D-tryptophan and in step VIII butyl(2-pyridin-2-ylethyl)amine (example 21) was used instead of (3-phenylpropyl)-(2-pyridin-2-ylethyl)amine. Cleavage from the resin was done with 5 % TFA in DCM. The product was purified using preparative RP-HPLC purification to obtain the title compound with 37 % yield.

MS-ESI$^+$ (m/z): 506 $[M+H]^+$, 254 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.50 (1H, m), 7.86-7.75 (4H, m), 7.71 (1H, br s), 7.46-7.40 (4H, m), 7.27 (1H, m), 4.54-4.51 (1H, m), 3.61-3.44 (6H, m), 3.40 (2H, m), 3.33-3.29 (1H, m), 3.15-2.96 (5H, m), 2.93-2.90 (2H, m), 1.30-1.17 (2H, m), 1.14-1.06 (2H, m), 0.74-0.71 (3H, m).

Example 12

Synthesis of (2*R*)-*N*-benzyl-*N*-methyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 12

Step I

Fmoc-3-naphthalen-1-yl-D-alanine (200.0 mg, 437.5 g/mol, 0.46 mmol, 1 eq) and DIPEA (79 µl, 129.12 g/mol, 0.755 g/cm^3, 0.46 mmol, 1 eq.) were dissolved in 1 ml of dry DCM. A solution of HATU (174 mg, 380.2 g/mol, 0.46 mmol, 1 eq.) in dry DCM (1 ml) was added and the mixture was stirred at ambient temperature for 15 minutes. A solution of *N*-methylbenzylamine (60 µl, 121.8 g/mol, 0.94 g/cm^3, 0.46 mmol, 1 eq) in dry DCM was added to the reaction mixture and the solution was stirred overnight at ambient temperature. 50 ml of DCM was then added to the reaction mixture and the mixture was washed twice with 20 ml of 5 % aq $NaHCO_3$. The organic phase was dried with

Na_2SO_4 and evaporated. The compound was purified with flash chromatography yielding 0.211 g (85 %) of pure (2*R*)-Fmoc-2-amino-*N*-benzyl-*N*-methyl-3-naphthalen-1-ylpropionamide.

MS-ESI$^+$ (m/z): 541 $[M+H]^+$

Step II

(2*R*)-Fmoc-2-amino-*N*-benzyl-*N*-methyl-3-naphthalen-1-ylpropionamide (0.211 g, 540.7 g/mol, 39 mmol) was dissolved in 10 ml of 25 % (v/v) piperidine/ACN –solution. After overnight stirring, the reaction mixture was evaporated and the product was purified with flash chromatography. The product, (2*R*)-2-amino-*N*-benzyl-*N*-methyl-3-naphthalen-1-ylpropionamide, was collected with a quantitative yield.

MS-ESI$^+$ (m/z): 319 $[M+H]^+$

Step III

(2*R*)-2-Amino-*N*-benzyl-*N*-methyl-3-naphthalen-1-ylpropionamide (65 mg, 318.4 g/mol, 0.20 mmol, 1 eq.) and DIPEA (35 µl, 129.2 g/mol, 0.20 mmol, 1eq.) were dissolved in dry THF (2 ml) under argon. 4-Nitrophenyl chloroformate (42 mg, 201.6 g/mol, 0.20 mmol, 1 eq.) dissolved in 1 ml of dry THF was added to the stirred solution. After 40 minutes of stirring at ambient temperature, phenethyl(2-pyridin-2-ylethyl)amine (example 16, 92 mg, 226.3 g/mol, 0.40 mmol, 2 eq.) dissolved in 1 ml of dry THF was added to the reaction mixture. After 3 h, the mixture was evaporated to dryness, dissolved in ACN (0.5 ml) and purified with reversed phase flash chromatography, using an isocratic method (eluent 45 % aq ACN, column Supelco Discovery DSC-C18, 5g), which yielded 41 mg (36 %) of the product, (2*R*)-*N*-benzyl-*N*-methyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide.

MS-ESI$^+$ (m/z): 571 $[M+H]^+$

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.67-8.64 (1H, m), 8.35 (1H, d, J=8.1 Hz), 7.82 (d, 1H, J=7.9 Hz), 7.71 (1H, d, J=7.9 Hz), 7.60-7.56 (2H, m), 7.46 (1H, m), 7.36 (1H, m), 7.28 (4H, m), 7.22-7.19 (6H, m), 7.13 8 (3H, m), 4.36 (1H, m), 3.75-3.53 (4H, m), 3.46-3.21 (2H, m).

Example 13

Synthesis of (2*R*)-*N*-(1-phenylethyl)-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 13

Step I

Fmoc-3-naphthalen-1-yl-D-alanine (200.0 mg, 437.5 g/mol, 0.46 mmol, 1 eq) and 1-phenylethylamine (60 µl, 121.8 g/mol, 0.94 g/cm^3, 0.46 mmol, 1 eq) were coupled using the same coupling agents and procedure as

described in step I of example 12. After flash chromatography, 157 mg (63 %) of (2*R*)-Fmoc-2-amino-3-naphthalen-1-yl-*N*-(1-phenylethyl)propionamide was obtained.

MS-ESI$^+$ (m/z): 541 $[M+H]^+$

Step II

(2*R*)-Fmoc-2-amino-3-naphthalen-1-yl-*N*-(1-phenylethyl)propionamide (157 mg, 540.7 g/mol, 0.29 mmol) was dissolved in a 20 % (v/v) piperidine/ACN solution. After overnight stirring at ambient temperature the solvents were evaporated and the product was purified with silica flash chromatography using isocratic elution with 5% MeOH in DCM. The purification gave 58 mg (63 %) of the product, (2*R*)-2-amino-3-naphthalen-1-yl-*N*-(1-phenylethyl)propionamide.

MS-ESI$^+$ (m/z): 319 $[M+H]^+$

Step III

(2*R*)-2-Amino-3-naphthalen-1-yl-*N*-(1-phenylethyl)propionamide (58 mg, 318.4 g/mol, 0.18 mmol, 1 eq) was reacted with 4-nitrophenyl chloroformate (37 mg, 201.6 g/mol, 0.18 mmol, 1 eq.) and phenethyl(2-pyridin-2-ylethyl)amine (example 16, 74 mg, 226.3 g/mol, 0.36 mmol, 2 eq.) to give the target urea compound as described in step III of example 12. After silica flash chromatography, 32 mg (31 %) of pure (2*R*)-3-naphthalen-1-yl-*N*-(1-phenylethyl)-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide was collected.

MS-ESI$^+$ (m/z): 571 $[M+H]^+$

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.45 (1H, m), 8.24 (1H, m), 7.81 (1H, m), 7.65-7.75 (1H, m), 7.53 (1H, m), 7.47 (2H, m), 7.38 (1H, m), 7.27-7.16 (7H, m), 7.11 (3H, m), 7.00-6.96 (3H, m), 4.98-4.89 (1H, m), 4.66 (1H, m), 3.56-3.49 (3H, m), 3.47-3.27 (3H, m), 2.87 (2H, m), 2.74 (2H, m), 1.31 (2H, d, J=6.8 Hz), 1.09 (1H, d, J=6.8 Hz).

Example 14

Synthesis of (2*R*)-*N*-cyclohexyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 14

Step I

Fmoc-3-naphthalen-1-yl-D-alanine (200.0 mg, 437.5 g/mol, 0.46 mmol, 1 eq) and cyclohexylamine (52 µl, 99.2 g/mol, 0.867 g/cm^3, 0.46 mmol, 1 eq) were coupled using the same coupling agents and procedure as described in step I of example 12. After workup, the crude (2*R*)-Fmoc-2-amino-

N-cyclohexyl-3naphthalen-1-ylpropionamide was used in the next step without purification.

MS-ESI$^+$ (m/z): 519 $[M+H]^+$, 541 $[M+Na]^+$

Step II

The crude product from step I was dissolved in a 20 % piperidine/DMF solution. After overnight stirring at ambient temperature the solvents were evaporated and the product was purified with silica flash chromatography as in step II in example 12. Pure fractions were pooled and evaporated giving 79 mg (58 % overall for steps I and II) of (2*R*)-2-amino-*N*-cyclohexyl-3-naphthylpropionamide.

Step III

(2*R*)-2-Amino-*N*-cyclohexyl-3-naphthalen-1-ylpropionamide (79 mg, 296.4 g/mol, 0.27 mmol, 1 eq.) was reacted with 4-nitrophenyl chloroformate (54 mg, 201.6 g/mol, 0.27 mmol, 1 eq.) and phenethyl(2-pyridin-2-ylethyl)amine, (example 16, 98 mg, 226.3 g/mol, 0.54 mmol, 2 eq.) to give the target urea compound as described in step III of example 12. After RP-HPLC purification, 51 mg (35 %) of pure (2*R*)-*N*-cyclohexyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide was collected.

MS-ESI$^+$ (m/z): 549 $[M+H]^+$

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.54 (1H, m), 8.29 (1H, m), 7.83 (1H, m), 7.73-7.71 (1H, m), 7.58 –7.54 (2H, m), 7.49-7.46 (1H, m), 7.36 (2H, m), 7.28-7.26 (1H, m), 7.19 (1H, m), 7.15 (3H, m), 7.13-7.10 (1H, m), 7.07 (1H, m), 4.58 (1H, m), 3.45-3.39 (3H, m), 3.35-3.29 (3H, m), 2.93 (3H, m), 2.78 (3H, m), 1.68 (1H, m), 1.54-1.40 (5H, m), 1.27-1.16 (2H, m), 1.00 (1H, m), 0.87 (1H, m), 0.62 (1H, m).

Example 15

Synthesis of (2*R*)-*N*-isobutyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide, Compound 15

Step I

Fmoc-3-naphthalen-1-yl-D-alanine (200.0 mg, 437.5 g/mol, 0.46 mmol, 1 eq) and isobutylamine (47μl, 73.1 g/mol, 0.729 g/cm^3, 0.46 mmol, 1 eq) were coupled using the same coupling agents and procedure as described in step I of example 12. After workup, the crude (2*R*)-Fmoc-2-amino-*N*-isobutyl-3-naphthalen-1-ylpropionamide was used for the next step without purification.

MS-ESI$^+$ (m/z): 493 $[M+H]^+$, 515 $[M+Na]^+$

Step II

The crude product from step I was dissolved in a 20 % piperidine/MeOH solution. After overnight stirring at ambient temperature the solvents were evaporated and the product was purified with silica flash chromatography as in step II in example 12. Pure fractions were pooled and evaporated giving 64 mg (52 % overall for steps I and II) of (2*S*)-2-amino-*N*-isobutyl-3-naphthalen-1-ylpropionamide.

Step III

(2*R*)-2-Amino-*N*-isobutyl-3-naphthalen-1-ylpropionamide (79 mg, 296.4 g/mol, 0.27 mmol, 1 eq.) was reacted with 4-nitrophenyl chloroformate (54 mg, 201.6 g/mol, 0.27 mmol, 1 eq.) and phenethyl(2-pyridin-2-ylethyl)amine (example 16, 98 mg, 226.3 g/mol, 0.54 mmol, 2 eq.) to give the target urea compound as described in step III of example 12. After silica flash chromatography purification, 68 mg (60 %) of pure (2*R*)-*N*-isobutyl-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide was collected.

MS-ESI$^+$ (m/z): 497 $[M+H]^+$

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.51 (1H, m), 8.23 (1H, m), 7.81 (1H, m), 7.71 (1H, d, J=7.67 Hz), 7.54 (2H, m), 7.46 (1H, tr, J=7.67 Hz), 7.39-7.32 (2H, m), 7.26-7.23 (2H, m), 7.19-7.16 (1H, m), 7.13-7.08 (3H, m), 7.02 (1H, d, J=7.67 Hz), 4.63 (1H, m), 3.58-3.45 (4H, m), 3.41-3.27 (2H, m), 2.93-2.83 (4H, m), 2.76-2.73 (2H, m), 1.50-1.43 (1H, m), 0.68 (3H, m), 0.64 (3H, m).

Following examples 16 to 22 describe the synthesis of building blocks required in the synthesis of the compounds of the invention.

Example 16

Synthesis of phenethyl(2-pyridin-2-ylethyl)amine, Compound 16

Step I

Phenylacetic acid (1.04 g, 136.15 g/mol, 7.6 mmol) was dissolved in DCM (15 ml). DCC (1.57 g, 206.33 g/mol, 7.6 mmol, 1 eq) was added and the mixture stirred for 30 min after which 2-(2-aminoethyl)pyridine (1.0 ml, 122.17 g/mol, 1.027 g/ml, 8.41 mmol, 1.1 eq) was added and the mixture stirred over night. The formed precipitate was filtered and the filtrate washed with water and dried over Na_2SO_4. After evaporation, the product was purified using flash chromatography. The yield was 54 %.

Step II

The product from step I (0.93 g, 240.31 g/mol, 3.87 mmol) was dissolved in THF (20 ml) and BH_3-THF –complex (1 M, 11.6 ml, 3 eq) was added to reduce the carbonyl group. The reaction mixture was refluxed for two hours and then quenched by adding water (11.6 ml). The mixture was made acidic with conc. HCl (11.6 ml) and stirred for 30 min. The mixture was then made alkaline with NaOH solution (5M) and the product was extracted with ethyl acetate. Drying and evaporation of the organic fractions gave the title compound with 71 % yield.

MS-ESI$^+$ (m/z): 227 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.40 (1H, m), 7.73-7.70 (1H, m), 7.28-7.22 (4H, m), 7.17 (3H, m), 2.98-2.94 (4H, m), 2.88-2.85 (2H, m), 2.81-2.77 (2H, m).

Example 17

Synthesis of bis(2-pyridin-2-ylethyl)amine, Compound 17

Step I

Ethyl-2-pyridyl acetate (1.0 ml, 165.19 g/mol, 1.08 g/ml, 6.5 mmol) and 2-(2-aminoethyl)pyridine (0.80 ml, 122.17 g/mol, 1.027 g/ml, 6.7 mmol, 1.03 eq) were heated in a microwave oven at 200°C for 10 min. The product was purified using flash chromatography. The yield was 73 %.

Step II

Reduction was done as in example 16, except that 9 eq of borane-THF –complex was used. The yield was 41 %.

MS-ESI$^+$ (m/z): 228 $[M+H]^+$

^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 8.50 (2H, m), 7.58-7.55 (2H, m), 7.15 (2H, m), 7.11-7.08 (2H, m), 3.08-3.05 (4H, m), 2.99-2.96 (4H, m).

Example 18

Synthesis of 4-[2-(2-pyridin-2-ylethylamino)ethyl]phenylamine, Compound 18

The synthesis was carried out as in example 16, except that in step I 2-(4-aminophenyl)ethylamine was used instead of 2-(2-aminoethyl)pyridine. The yield for step I was 85 % and 88 % for step II.

MS-ESI$^+$ (m/z): 242 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.35 (1H, m), 7.72-7.68 (1H, m), 7.24-7.20 (2H, m), 6.95-6.90 (2H, m), 6.68-6.61 (2H, m), 3.07-3.04 (2H, m), 2.97 (2H, m), 2.92-2.88 (2H, m), 2.72-2.69 (2H, m).

Example 19

Synthesis of (2-cyclohexylethyl)-(2-pyridin-2-ylethyl)amine, Compound 19

The synthesis was carried out as in example 17, except that in step I ethyl cyclohexylacetate (2 eq) was used instead of ethyl-2-pyridyl acetate. In step II 3 eq of borane-THF –complex were used. The yield for step I was 67 % and 31 % for step II.

MS-ESI$^+$ (m/z): 233 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.44 (1H, m), 7.75-7.72 (1H, m), 7.31 (1H, m), 7.25-7.22 (1H, m), 2.95 (4H, m), 2.65-2.62 (2H, m), 1.70-1.67 (4H, m), 1.57 (1H, m), 1.41-1.37 (2H, m), 1.29-1.12 (4H, m), 0.95-0.87 (2H, m).

Example 20

Synthesis of (3-phenylpropyl)-(2-pyridin-2-ylethyl)amine, Compound 20

The synthesis was carried out as in example 16, except that in step I 3-phenylpropionic acid was used instead of phenylacetic acid. The yield for step I was 95 % and 64 % for step II.

MS-ESI$^+$ (m/z): 241 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.43 (1H, m), 7.74-7.70 (1H, m), 7.29-7.11 (7H, m), 2.96-2.89 (4H, m), 2.64-2.56 (4H, m), 1.83-1.77 (2H, m).

Example 21

Synthesis of butyl(2-pyridin-2-ylethyl)amine, Compound 21

The synthesis was carried out as in example 16, except that in step I butyric acid was used instead of phenylacetic acid. The yield for step I was 87 % and 49 % for step II.

MS-ESI$^+$ (m/z): 179 $[M+H]^+$

1H NMR (500 MHz, CD3OD, δ, ppm): 8.44 (1H, m), 7.75-7.72 (IH, m), 7.31 (1H, m), 7.26-7.23 (1H, m), 2.99 (4H, s), 2.68-2.65 (2H, m), 1.54-1.47 (2H, m), 1.38-1.28 (2H, m), 0.94-0.91 (3H, m).

Example 22

Synthesis of *N*,*N*-dimethyl-*N'*-(2-pyridin-2-ylethyl)ethane-1,2-diamine, Compound 22

The synthesis was carried out as in example 17, except that in step I 2-dimethylamino ethylamine (1 eq) was used instead of 2-(2-aminoethyl)pyridine. The yield for step I was 90 % and 57 % for step II.

MS-ESI$^+$ (m/z): 194 $[M+H]^+$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.47 (1H, m), 7.80-7.74 (1H, m), 7.41-7.25 (2H, m), 3.11-3.08 (2H, m), 3.05-3.01 (2H, m), 2.88-2.85 (2H, m), 2.59-2.54 (2H, m), 2.30 (3H, s), 2.28 (3H, s).

Example 23

Synthesis of (2S,2'R)-2-{2-[3,3-bis(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}-3-methylbutyramide, Compound 23

Step I

Fmoc-3-naphthalen-1-yl-D-alanine (2.01 g, 437.5 g/mol, 4.60 mmol, 1 eq) and DIPEA (783 µl, 129.12 g/mol, 0.755 g/cm^3, 4.6 mmol, 1 eq) were dissolved in 20 ml of dry DCM. DCC (0.95 g, 206.33 g/mol, 4.58 mmol, 1 eq) and HOBt (0.70 g, 153.12 g/mol, 4.58 mmol, 1 eq) was added before the mixture was stirred at ambient temperature for 15 minutes. A solution of L-valine amide hydrochloride (0.70 g, 152.7 g/mol, 4.58 mmol, 1 eq) and DIPEA (783 µl, 129.12 g/mol, 0.755 g/cm^3, 4.6 mmol, 1 eq) in dry DMF (20 ml) was added to the reaction mixture and the solution was stirred overnight at ambient temperature. Formed precipitation was filtered and washed with DCM. The compound was purified by slurrying the precipitation twice with MeOH (75 ml + 150 ml) after which the filtered precipitation was dried at ambient temperature yielding 1.84 g (75 %) of the product, (2R)-2-(Fmoc-2-amino-3-naphthalen-1-ylpropionylamino)-3-methylbutyramide.

MS-ESI$^+$ (m/z): 536 $[M+H]^+$

Step II

(2R)-2-(Fmoc-2-amino-3-naphthalen-1-ylpropionylamino)-3-methyl-butyramide (1.84 g, 535.6 g/mol, 3.43 mmol) was dissolved in a 20 % (v/v) piperidine/ACN solution (20 ml). After 1,5 h of stirring at ambient temperature, the solvents were evaporated and the residue was dissolved in DCM and washed twice with water and once with brine. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The product was purified with

silica flash chromatography using gradient elution from 1% MeOH to 10% MeOH in DCM. 0.5% Et_3N was added to the eluent. The purification gave 0.69 g (64 %) of the product, (2R)-2-(2-amino-3-naphthalen-1-ylpropionylamino)-3-methylbutyramide.

MS-ESI$^+$ (m/z): 314 $[M+H]^+$

Step III

(2R)-2-(2-Amino-3-naphthalen-1-ylpropionylamino)-3-methylbutyramide (0.52 g, 313.4 g/mol, 1.65 mmol, 1 eq) and DIPEA (0.57 ml, 129.2 g/mol, 0.755 g/cm^3, 3.33 mmol, 2 eq) were dissolved in dry THF (25 ml). 4-Nitrophenyl chloroformate (0.34 g, 201.6 g/mol, 1.68 mmol, 1 eq) was added to the stirred solution. After 30 minutes at ambient temperature, a solution of bis(2-pyridin-2-ylethyl)amine (example 17, 1.31 g, 227.3 g/mol, 5.78 mmol, 3.5 eq) and DIPEA (0.99 ml, 129.2 g/mol, 0.755 g/cm^3, 5.79 mmol, 3.5 eq) dissolved in 10 ml of dry THF was added to the reaction mixture. After overnight stirring, the mixture was evaporated to dryness. The product was purified first with silica flash chromatography (gradient elution from 1% MeOH to 10% MeOH in DCM) and then with reversed phase flash chromatography (gradient elution from water to 50% aq ACN, column Supelco Discovery DSC-C18, 10g), which yielded 0.35 g (38 %) of (2S,2'R)-2-{2-[3,3-bis(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}-3-methylbutyramide.

MS-ESI$^+$ (m/z): 567 $[M+H]^+$, 284 $[M+2H]^{2+}$

^{1}H NMR (500 MHz, CD_3OD, δ, ppm): 8.45 (2H, m, J = 5.01 Hz), 8.20 (1H, d, J = 8.08 Hz), 7.87-7.84 (1H, d, J = 8.08 Hz), 7.76-7.73 (1H, d, J = 8.08 Hz), 7.71-7.67 (2H, m, J = 7.60 Hz), 7.57-7.53 (1H, m, J = 6.95 Hz), 7.50-7.46 (1H, m, J = 8.08 Hz), 7.42 (1H, m, J = 6.95 Hz), 7.38-7.35 (1H, m, J = 7.27 Hz), 7.22 (2H, m, J = 5.01 Hz, J = 7.60 Hz), 7.17 (2H, m), 4.68-4.65 (1H, m, J = 7.60 Hz), 4.09 (1H, d), 3.64-3.59 (1H, m, J = 7.60 Hz), 3.52-3.46 (3H, m, J = 7.27 Hz), 3.44-3.37 (2H, m, J = 7.27 Hz), 2.89-2.85 (4H, t, J = 7.27 Hz), 2.07-2.00 (1H, m, J = 6.95 Hz), 0.69-0.66 (3H, d, J = 6.95 Hz), 0.64-0.61 (3H, d, J = 6.95 Hz).

Example 24

Additional compounds (including but not restricted to those described below) were prepared according to methods described in the examples 1 to 22 by using corresponding starting materials.

Compound No.	Name	MS-ESI+ (m/z)	Example no.
24	(2*R*, 2'*R*)-5-Guanidino-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	624	1
25	(2*R*, 2'*R*)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-3-pyridin-3-ylpropionamide	615	1
26	(2*S*,2'*R*)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-3-phenylpropionamide	614	1
27	(2*S*, 2'*R*)-2-{2'-[3,3-Bis(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}-4-methylpentanamide	581	1
28	(2*R*, 2'*R*)-5-Amino-2-{3'-naphthalen-1-yl-2'-[3-(3-phenylpropyl)-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-pentanamide	595	1
29	(2*R*, 2'*R*)-5-Amino-2-{2'-[3-(4-methylbenzyl)-3-(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-yl-propionylamino}-pentanamide	581	1
30	(2*R*, 2'*R*)-3-(4-guanidinophenyl)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-propionamide	671	1
31	(2*S*, 2'*R*)-3-(1*H*-indol-3-yl)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-propionamide	653	1
32	(2*R*, 2'*R*)-)5-Guanidino-2-{3'-(1*H*-indol-3-yl)-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	612	1
33	(2*R*, 2'*S*)-5-Amino-2-{3'-biphenyl-4-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	607	1
34	(2*R*, 2'*R*)-5-Amino-2-{2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]-3'-phenylpropionylamino}pentanamide	531	1
35	(3*S*, 2'*R*)-3-{3'-Naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-5-phenylpentanamide	642	1
36	(2*S*, 2'*R*)-2-{*N*-methyl-3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-3-phenylpropionamide	628	1
37	(2*R*, 2'*R*)-5-Amino-2-{3',3'-diphenyl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	607	1
38	(2*R*)-*N*-(3-Aminopropyl)-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide	524	10

39	(2*R*)-*N*-(4-Aminomethylbenzyl)-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide	586	10
40	(2*R*)-*N*-(2-Amino-1,1-dimethylethyl)-3-naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamide	538	10
41	(2*R*, 2'*R*)-5-Amino-2-{2'-[3-butyl-3-(2-pyridin-2-ylethyl)ureido]-3'-naphthalen-1-ylpropionylamino}pentanamide	533	1
42	(2*R*, 2'*R*)-5-Amino-2-{3'-naphthalen-1-yl-2'-[3-(2-phenyl-propyl)-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-pentanamide	595	1
43	(2*R*)-2-{3-[2-(2-Methoxyphenyl)ethyl]-3-(2-pyridin-2-ylethyl)ureido}-3-naphthalen-1-yl-propionamide	497	10
44	(2*R*, 2'*R*)-5-Amino-2-(2'-{3-[3-(6-methylpyridin-2-yl)-propyl]-3-phenethylureido}-3'-naphthalen-1-ylpropionylamino)-pentanamide	609	1
45	(2*R*, 2'*R*)-5-Amino-2-(2'-{3-[3-(4-methylpiperazin-1-yl)propyl]-3-phenethylureido}-3-naphthalen-1-ylpropionyl-amino)pentanamide	616	1
46	(2*S*, 2'*R*)-4-Methylsulfanyl-2-[3'-naphthalen-1-yl-2'-(3-phenethyl-3-pyridin-3-ylmethylureido)propionylamino]-butyramide	584	1
47	(2*R*)-*N*-(3-Aminomethylcyclohexylmethyl)-2-(3,3-diphenethylureido)-3-naphthalen-1-ylpropionamide	591	10
48	(2*R*, 2'*R*)-5-Amino-2-{2'-[3-methyl-3-(2-pyridin-2-ylethyl)-ureido]-3'-naphthalen-1-ylpropionylamino}pentanamide	491	1
49	(2*R*)-3-Naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-4-ylethyl)ureido]propionamide	467	1
50	(2*R*, 2*R*)-5-Amino-2-{2'-[3-(2-dimethylaminoethyl)-3-phenethylureido]-3'-naphthalen-1-ylpropionylamino}-pentanamide	547	1
51	(2*R*)-3-Naphthalen-1-yl-2-[3-phenethyl-3-(2-pyridin-3-ylethyl)ureido]propionamide	467	1
52	(2*R*, 2'*R*)-5-Amino-2-[3'-naphthalen-1-yl-2'-(3-phenethyl-3-pyridin-2-ylmethylureido)propionylamino]pentanamide	567	1
53	(2*R*, 2'*R*)-5-Amino-2-{2'-[3-(6-methylpyridin-2-ylmethyl)-3-phenethylureido]-3'-naphthalen-1-ylpropionylamino}-pentanamide	581	1
54	(2*R*, 3'*R*)-5-Guanidino-2-{4'-naphthalen-1-yl-3'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]butyrylamino}pentanamide	637	1
55	(2*R*, 2'*R*)-3-(1*H*-imidazol-4-yl)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamino}-	604	1

	propionamide		
56	(2'*R*)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamino}-3-piperidin-4-ylpropionamide	621	1
57	(2*R*, 2'*R*)-3-(1*H*-indol-3-yl)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionamino}-propionamide	653	1
58	(2*S*, 2'*R*)-4-Hydroxy-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}butyramide	568	1
59	(2*S*, 2'*R*)-3-(4-Hydroxyphenyl)-2-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-propionamide	630	1
60	(3*S*, 2'*R*)-4-(1*H*-Indol-3-yl)-3-{3'-naphthalen-1-yl-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}-butyramide	667	1
61	(2*R*, 2'*R*)-5-Amino-2-{3'-(4-benzyloxyphenyl)-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	637	1
62	(2*R*, 2'*S*)-5-Amino-2-{2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]-3'-pyridin-3-yl-propionylamino}pentanamide	532	1
63	(2*R*, 2'*R*)-5-Amino-2-{3'-(4-benzoylphenyl)-2'-[3-phenethyl-3-(2-pyridin-2-ylethyl)ureido]propionylamino}pentanamide	635	1

Example 25

Binding affinity at the human somatostatin receptor subtypes

The affinity of the compounds of the invention for the five human somatostatin receptor subtypes (SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5) was determined in competition binding assays with (^{125}I-Tyr)-[Leu^{8},DTrp^{22}]-somatostatin-28 (^{125}I-LTT-SRIF-28). The biological material for these experiments consisted of membranes from Chinese hamster ovary (CHO) cells stably transfected with one of the five human somatostatin receptor subtypes. Membranes (3-20 µg of total protein per sample) and trace amount of ^{125}I-LTT-SRIF-28 were incubated in 10 mM Hepes, 1 mM EDTA, 5 mM $MgCl_2$, 5 mg/ml of BSA and 30 µg/ml bacitracin, pH 7.6 with six concentrations of the compounds. Each concentration was run in duplicate. Non-specific binding was defined by 1 µM somatostatin-14 (SRIF-14) and corresponded to 5-25% of total binding. After 60 min at room temperature, incubations were terminated by rapid vacuum filtration through GF/B glass fiber filter mats (presoaked at 4°C in 200 ml of 10 mM Hepes, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.6) and three 5

ml washes with ice-cold wash buffer (20 mM TRIS, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4). The filters were then dried, impregnated with scintillate and their radioactivity was measured by scintillation counting. The analysis of the experiments was carried out by non-linear least square curve fitting. Affinity constants (K_i) were calculated from the IC_{50}-values according to the Cheng-Prusoff equation (Cheng and Prusoff, 1973). Experiments were repeated a minimum of three times.

Using the aforementioned protocol, the following test results were obtained.

Compound	K_i (SSTR1) / nM	K_i (SSTR2) / nM	K_i (SSTR3) / nM	K_i (SSTR4) / nM	K_i (SSTR5) / nM
Compound 3	19 ± 1	>10000	>10000	640 ± 200	>10000
Compound 1	28 ± 4	>10000	>10000	890 ± 90	>10000
Compound 6	64 ± 10	>10000	>3000	550 ± 180	>10000

Besides these, a large set of compounds had a K_i-value less than 100 nM for SSTR1. Among this set were for example:

Compound 2
Compound 4
Compound 5
Compound 7
Compound 14
Compound 24
Compound 25
Compound 26
Compound 27
Compound 28
Compound 29
Compound 30
Compound 31

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the expert skilled in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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